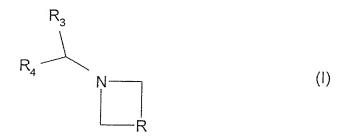
Amendment Pursuant to 37 C.F.R. § 1.121

IN THE CLAIMS:

The claims set forth below with amendments as indicated will replace all prior versions and listing of claims in the application.

(currently amended) A combination composition comprising one or more products
which activate dopaminergic neurotransmission in the brain a dopaminergic
agonist and of one or more CB1 antagonist azetidine derivatives of formula I:



wherein

either A:

R is CR_1R_2 , $C=C(R_5)SO_2R_6$ or $C=C(R_7)SO_2$ alk; wherein

either R_1 is hydrogen and R_2 is $-C(R_8)(R_9)(R_{10})$, $-C(R_8)(R_{11})(R_{12})$,

-CO-NR $_{13}$ R $_{14}$, -CH $_2$ -CO-NR $_{13}$ R $_{14}$, -CH $_2$ -CO-R $_6$, -CO-cycloalkyl,

 $-SO-R_6, -SO_2-R_6, -C(OH)(R_{12})(R_6), -C(OH)(R_6)(alkyl), -C(=NOalk)R_6, \\$

 $-C(=\!NO\!-\!CH_2\!-\!CH\!=\!CH_2)R_6, -CH_2\!-\!CH(R_6)NR_{31}R_{32}, -CH_2\!-\!C(=\!NOalk)R_6, -CH_2\!-\!CH_2)R_6, -CH_2\!-\!CH_2$

-CH(R_6)NR₃₁R₃₂, -CH(R_6)NHSO₂alk, -CH(R_6)NHCONHalk or

-CH(R₆)NHCOalk; or

 R_1 is alkyl, NH-R $_{\!15}$, cyano, -S-alk-NR $_{\!16}R_{17}$, -CH $_{\!2}$ -NR $_{\!18}R_{19}$ or -NR $_{\!20}R_{21}$; and

 R_2 is $-C(R_8)(R_{11})(R_{12})$;

R₃ and R₄, which are identical or different, independently are either alkyl, cycloalkyl, aryl chosen from phenyl, naphthyl or indenyl, wherein aryl being unsubstituted or substituted by one or more halogen, alkyl, alkoxy,

formyl, hydroxyl, trifluoromethyl, trifluoromethoxy, -CO-alk, cyano, -COOH, -COOalk, -CONR $_{22}$ R $_{23}$, -CO-NH-NR $_{24}$ R $_{25}$, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, hydroxyalkyl or -alk-NR $_{24}$ R $_{25}$; or heteroaryl chosen from benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, 2,3-dihydroxybenzofuryl, 2,3-dihydrobenzothienyl, furyl, imidazolyl, isochromanyl, isoquinolyl, pyrrolyl, pyridyl, pyrimidinyl, quinolyl, 1,2,3,4-tetrahydroisoquinolyl, thiazolyl and thienyl, wherein heteroaryl is unsubstituted or substituted by one or more halogen, alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, -COOH, -COOalk, -CO-NH-NR $_{24}$ R $_{25}$, -CONR $_{22}$ R $_{23}$, -alk-NR $_{24}$ R $_{25}$, alkylsulfanyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl or hydroxyalkyl;

R₅ is hydrogen or alkyl;

 R_6 is Ar_1 or Het_1 ;

R₇ is cycloalkyl, heterocycloalkyl or heterocyclenyl optionally substituted by -CSO-phenyl;

R₈ is hydrogen or alkyl;

 R_9 is -CO-NR₂₆R₂₇, -COOH, -COOalk, -CH₂OH, -NH-CO-NH-alk, -CH₂-NHR₂₈ or -NHCOOalk;

 R_{10} is Ar_1 or Het_1 ;

R₁₁ is -SO₂-alk, -SO₂-Ar₁ or -SO₂-Het₁;

R₁₂ is hydrogen, Ar₁ or Het₁;

R₁₃ is hydrogen or alkyl;

 R_{14} is Ar_1 , Het_1 , -alk- Ar_1 or -alk- Het_1 ;

 R_{15} is alkyl, cycloalkyl or -alk-NR₂₉R₃₀;

 R_{16} and R_{17} , which are identical or different, independently are either hydrogen or alkyl; or

 R_{16} and R_{17} taken together with the nitrogen atom to which they are attached form a saturated or unsaturated 3 to 10 ring membered mono- or 5 to 10 ring membered bicyclic heterocycle, optionally comprising one or more other heteroatoms chosen from oxygen, sulfur and nitrogen and optionally substituted by one or more alkyl;

R₁₈ is hydrogen or alkyl;

- R₁₉ is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, cycloalkylcarbonyl, -SO₂alk, -CO-NHalk or -COOalk; or
- R₁₈ and R₁₉ taken with the nitrogen atom to which they are attached form a saturated or unsaturated 3 to 10 ring membered mono- or 5 to 10 ring membered bicyclic heterocycle, optionally comprising one or more heteroatoms chosen from oxygen, sulfur and nitrogen and optionally substituted by one or more alkyl;
- -NR₂₀R₂₁ is a saturated or unsaturated monocyclic heterocycle having 3 to 8 ring members and optionally comprising another heteroatom chosen from oxygen, nitrogen and sulfur;
- R_{22} and R_{23} , which are identical or different, independently are hydrogen or alkyl; or
- R₂₂ and R₂₃ taken together with the nitrogen atom to which they are attached form a saturated mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one more alkyl;
- R₂₄ and R₂₅, which are identical or different, independently are hydrogen, alkyl, -COOalk, cycloalkyl, alkylcycloalkyl, -alk-O-alk or hydroxyalkyl; or
- R₂₄ and R₂₅ taken together with the nitrogen atom to which they are attached form a saturated or unsaturated and mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or

more alkyl, -COalk, -CO-NHalk, -CS-NHalk, oxo, hydroxyalkyl, -alk-O-alk or -CO-NH₂;

- R₂₆ and R₂₇, which are identical or different, independently are hydrogen, alkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, -alk-COOalk, -alk-Ar₁, alk-Het₁, Het₁ or -alk-N(alk)₂; or
- R₂₆ and R₂₇ taken together with the nitrogen atom to which they are attached form a saturated or unsaturated and mono- or bicyclic heterocycle having 3 to 10 ring members and optionally comprising one or more heteroatoms chosen from oxygen, sulfur and nitrogen and optionally substituted by one or more alkyl, alkoxy or halogen;
- R₂₈ is -CH₂-alk, benzyl, -SO₂alk, -CONHalk, -COalk, cycloalkylalkylcarbonyl, cycloalkylcarbonyl or -CO-(CH₂)_nOH, wherein n is an integer from 1 to 3;
- R_{29} and R_{30} , which are identical or different, independently are hydrogen or alkyl; or
- R₂₉ and R₃₀ taken together with the nitrogen atom to which they are attached form a saturated mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl radicals;
- R_{31} and R_{32} , which are identical or different, independently are hydrogen, alkyl, Ar_1 or -alk- Ar_1 ; or
- R₃₁ and R₃₂ taken together with the nitrogen atom to which they are attached form a heterocycle chosen from aziridinyl, azetidinyl, pyrrolidinyl and piperidinyl;
- Ar₁ is phenyl or naphthyl optionally substituted by one or more substituents chosen from halogen, alkyl, alkoxy, -CO-alk, cyano, -COOH, -COOalk, -CONR₂₂R₂₃, -CO-NH-NR₂₄R₂₅, alkylsulfanyl, alkylsulfinyl, alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, hydroxyalkyl, -alk-NR₂₄R₂₅, -NR₂₄R₂₅, alkylthioalkyl, formyl, hydroxyl, CF₃, OCF₃, Het₁, O-alk-NH-cycloalkyl or SO₂NH₂;

Het₁ is a saturated or unsaturated and mono- or bicyclic heterocycle having 3 to 10 ring members and comprising one or more heteroatoms chosen from oxygen, sulfur and nitrogen and optionally substituted by one or more halogen, alkyl, alkoxy, alkoxycarbonyl, -CONR₂₂R₂₃, hydroxyl, hydroxyalkyl, oxo or SO₂NH₂;

or B: wherein

R is CHR₃₃; wherein

 R_{33} is -NHCOR₃₄ or -N(R_{35})-Y- R_{36} ;

Y is CO or SO_2 ;

R₃ and R₄, which are identical or different, are either aryl chosen from phenyl, naphthyl and indenyl, wherein aryl being unsubstituted or substituted by one or more halogen, alkyl, alkoxy, formyl, hydroxyl, trifluoromethyl, trifluoromethoxy, -CO-alk, cyano, -COOH, -COOalk, -CONR₃₇R₃₈, -CO-NH-NR₃₉R₄₀, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfonylalkyl, hydroxyalkyl or -alk-NR₃₇R₃₈; or heteroaryl chosen from benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, 2,3-dihydro-benzofuryl, 2,3-dihydro-benzothienyl, pyrimidinyl, furyl, imidazolyl, isochromanyl, isoquinolyl, pyrrolyl, pyridyl, quinolyl, 1,2,3,4-tetrahydroisoquinolyl, thiazolyl and thienyl, wherein heteroaryl being unsubstituted or substituted by halogen, alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, -COOH, -COOalk, -CO-NH-NR₃₉R₄₀, -CONR₃₇R₃₈, -alk-NR₃₉R₄₀, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, or hydroxyalkyl;

R₃₄ is -alk-SO₂-R₄₁, -alk-SO₂-CH=CH-R₄₁, Het₂ substituted by -SO₂-R₄₁ or phenyl substituted by -SO₂-R₄₁ or -alk-SO₂-R₄₁;

R₃₅ is hydrogen or alkyl;

R₃₆ is phenylalkyl, Het₂ or Ar₂;

 R_{37} and R_{38} , which are identical or different, independently are hydrogen or alkyl; or

R₃₇ and R₃₈ taken together with the nitrogen atom to which they are attached form a saturated mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl;

R₃₉ and R₄₀, which are identical or different, independently are hydrogen or alkyl, -COOalk, cycloalkyl, alkylcycloalkyl, -alk-O-alk or hydroxyalkyl; or

R₃₉ and R₄₀ taken together with the nitrogen atom to which they are attached form a saturated or unsaturated and mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl, -COalk, -COOalk, -CO-NHalk, -CS-NHalk, oxo, hydroxyalkyl, -alk-O-alk or -CO-NH₂;

R₄₁ is alkyl, Ar₂ or Het₂;

Ar₂ is phenyl, naphthyl or indenyl radical, these radicals optionally being substituted by one or more halogen, alkyl, alkoxy, cyano, -CO-alk, -COOH, -COOalk, -CONR₄₂R₄₃, -CO-NH-NR₄₄R₄₅, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, -alk-NR₄₄R₄₅, -NR₄₄R₄₅, alkylthioalkyl, formyl, hydroxyl, hydroxyalkyl, Het₂, -O-alk-NH-cycloalkyl, OCF₃, CF₃, -NH-CO-alk, -SO₂NH₂, -HN-COCH₃, -NH-COOalk or Het₂ or else on two adjacent carbon atoms by a dioxymethylene;

Het₂ is a saturated or unsaturated and mono- or bicyclic heterocycle having 3 to 10 ring members and comprising one or more heteroatoms chosen from oxygen, sulfur and nitrogen optionally substituted by one or more alkyl, alkoxy, vinyl, halogen, alkoxycarbonyl, oxo, hydroxyl, OCF₃ or CF₃, the nitrogenous heterocycles optionally being in their N-oxidized form;

 R_{42} and R_{43} , which are identical or different, independently are hydrogen or alkyl;

or

R₄₂ and R₄₃ taken together with the nitrogen atom to which they are attached form a saturated mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl;

R₄₄ and R₄₅, which are identical or different, independently are hydrogen, alkyl, -COOalk, cycloalkyl, alkylcycloalkyl, -alk-O-alk or hydroxyalkyl; or

R₄₄ and R₄₅ taken together with the nitrogen atom to which they are attached form a saturated or unsaturated and mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl, -COalk, -COOalk, -CO-NHalk, -CS-NHalk, oxo, hydroxyalkyl, -alk-O-alk or -CO-NH₂;

or C: wherein R is CHR₄₆, wherein

 R_{46} is $-N(R_{47})R_{48}$, $-N(R_{47})-CO-R_{48}$ or $-N(R_{47})-SO_2R_{49}$;

R₃ and R₄, which are identical or different, represent either an aryl chosen from phenyl, naphthyl and indenyl, wherein aryl being unsubstituted or substituted by one or more halogen, alkyl, alkoxy, formyl, hydroxyl, trifluoromethyl, trifluoromethoxy, -CO-alk, cyano, -COOH, -COOalk, -CONR₅₀R₅₁, -CO-NH-NR₅₂R₅₃, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, hydroxyalkyl or -alk-NR₇R₈; or a heteroaryl chosen from benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, 2,3-dihydrobenzofuryl, 2,3-dihydrobenzothienyl, furyl, imidazolyl, isochromanyl, isoquinolyl, pyrrolyl, pyridyl, pyrimidyl, quinolyl, 1,2,3,4-tetrahydroisoquinolyl, thiazolyl and thienyl, wherein heteroaryl being unsubstituted or substituted by halogen, alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, -COOH, -COOalk, -CO-NH-NR₅₂R₅₃, -CONR₅₀R₅₁, -alk-NR₅₂R₅₃, alkylsulfanyl,

- alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl or hydroxyalkyl;
- R_{47} is $-C(R_{54})(R_{55})$ -Het₃, Het₃, $-C(R_{54})(R_{55})$ -Ar₃, Ar₃, cycloalkyl or norbornyl;
- R₄₈ is hydrogen or hydroxyalkyl, -alk-COOalk, -alk-CONR₅₀R₅₁, -alk-NR₅₀R₅₁, alkoxy; Ar₃, Het₃, -CH₂Ar₃, -CH₂Het₃ or alkyl, optionally substituted with one or more halogen;
- R₄₉ is hydroxyalkyl, -alk-COOalk, -alk-CONR₅₀R₅₁, -alk-NR₅₀R₅₁, alkoxy, Ar₃, Het₃, -CH₂Ar₃, -CH₂Het₃ or alkyl optionally substituted with one or more halogen;
- R_{50} and R_{51} , which are identical or different, independently are hydrogen or alkyl; or
- R₅₀ and R₅₁ taken together with the nitrogen atom to which they are attached form a saturated mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl;
- R₅₂ and R₅₃, which are identical or different, independently are hydrogen or alkyl, -COOalk, cycloalkyl, alkylcycloalkyl, -alk-O-alk or hydroxyalkyl; or
- R₅₂ and R₅₃ taken together with the nitrogen atom to which they are attached form a saturated or unsaturated and mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl, -COalk, -COOalk, -CO-NHalk, -CS-NHalk, oxo, hydroxyalkyl, -alk-O-alk or -CO-NH₂;
- R_{54} is hydrogen, hydroxyalkyl, -alk-COOalk, -alk-CONR₅₀R₅₁, -alk-NR₅₀R₅₁, alkoxyalkyl, Ar₃, Het₃, -CH₂Ar₃, -CH₂Het₃ or alkyl optionally substituted with one or more halogen;
- R₅₅ is hydrogen or hydroxyalkyl, -alk-COOalk, -alk-CONR₅₀R₅₁, -alk-NR₅₀R₅₁, alkoxyalkyl or alkyl optionally substituted with one or more halogen; or

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Examiner: Chong, Yong Soo

R₅₄ and R₅₅ taken together with the carbon atom to which they are attached form a saturated mono- or bicyclic ring having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl;

- Ar₃ is phenyl, naphthyl or indenyl, optionally being substituted by one or more halogen, alkyl, alkoxy, -CO-alk, cyano, -COOH, -COOalk, -CONR₅₆R₅₇, -CO-NH-NR₅₈R₅₉, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, -alk-NR₅₈R₅₉, -NR₅₈R₅₉, alkylthioalkyl, formyl, CF₃, OCF₃, Het₃, -O-alk-NHcycloalkyl, SO₂NH₂, hydroxyl, hydroxyalkyl, -NHCOalk or -NHCOOalk or on 2 adjacent carbon atoms by dioxymethylene;
- Het₃ is a saturated or unsaturated and mono- or bicyclic heterocycle having 3 to 10 ring members and comprising one or more heteroatoms chosen from oxygen, sulfur and nitrogen optionally substituted by one or more alkyl, alkoxy, halogen, alkoxycarbonyl, oxo or hydroxyl, the nitrogenous heterocycles optionally being in their N-oxidized form;
- R₅₆ and R₅₇, which are identical or different, independently are hydrogen or alkyl radical; or
- R₅₆ and R₅₇ taken together with the nitrogen atom to which they are attached form a saturated mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl;
- R₅₈ and R₅₉, which are identical or different, independently are hydrogen or alkyl; or
- R₅₈ and R₅₉ taken together with the nitrogen atom to which they are attached form a saturated mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl;

alk is an alkyl or alkylene radical; and wherein

the alkyl, alkylene and alkoxy radicals have straight or branched chains and comprise 1 to 6 carbon atoms, the cycloalkyl radicals comprise 3 to 10 carbon atoms and the heterocycloalkyl and heterocyclenyl radicals comprise 3 to 10 carbon atoms; or an optical isomer thereof or a pharmaceutically acceptable salt thereof.

2. (currently presented) The combination composition according to claim 1, wherein the compound of formula (I) is chosen from the following compounds: N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(pyrid-3-yl)methylsulfonamide or N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide, or a pharmaceutically acceptable salt thereof.

3. - 9. (canceled)

10. (currently presented) The combination composition according to claim 1, wherein the product which activates dopaminergic neurotransmission in the brain dopaminergic agonist is levodopa and the CB1 antagonist is N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl)-methylsulfonamide.

11. - 19. (canceled)

- 20. (currently amended) A pharmaceutical composition comprising one or more products which activate dopaminergic neurotransmission in the brain a dopaminergic agonist and one or more CB1 antagonists of formula (I) as defined in claim 1 in combination with a compatible and pharmaceutically acceptable vehicle.
- 21. (**original**) The pharmaceutical composition according to claim 20, wherein the compound of formula (I) as defined in claim 1 is chosen from the following compounds:

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(pyrid-3-yl)methylsulfonamide, or

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide, or a pharmaceutically acceptable salt thereof.

22. - 28. (canceled)

29. (currently amended) The pharmaceutical composition according to claim 20, wherein the product which activates dopaminergic neurotransmission in the brain dopaminergic agonist is levodopa and the CB1 antagonist is N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide.

30. - 34. (canceled)

- 35. (**original**) The pharmaceutical composition according to claim 20 for a simultaneous use, separate use or use spread out over time.
- 36. (**original**) The pharmaceutical composition according to claim 20 wherein the CB1 antagonist of formula (I) as defined in claim 1 is present in an amount of from about 0.1 mg to about 500 mg.